REMARKS/ARGUMENTS

Present Invention and Pending Claims

Claims 1-8 and 15-23 are pending. Claims 1-8 are directed to a pharmaceutical composition. Claims 15-23 are directed to a method of treating a cardiovascular disorder.

Summary of the Claim Amendments

The element of claim 11 has been added to claims 1 and 5. Claims 9-14 have been canceled. In view of the amendment to claim 1, claims 18-23 have been amended to delete the redundant reference to *S*-[2-([[1-(2-ethylbutyl)cyclohexyl]carbonyl]amino)phenyl] 2-methylpropanethioate. No new matter has been added by way of these amendments.

Summary of the Office Action

Claims 1-9 and 11-23 have been rejected under 35 U.S.C. § 103(a), as allegedly obvious over Gumkowski et al. (U.S. Patent Application Publication 2006/0014788) in view of Ault et al. (U.S. Patent 7,049,283) and Englert et al. (U.S. Patent 6,723,751). Claims 1-9 and 11-23 have been rejected for nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-24 of Shinkai et al. II (U.S. Patent 6,753,346) in view of Ault et al. (U.S. Patent 7,049,283). Reconsideration of the pending claims is hereby requested.

Preliminary Matters

The Examiner notes on page 2 of the Office Action that the specie election regarding the type of cardiovascular disorder is withdrawn and that all claimed disorders are under examination. Applicants thank the Examiner for the withdrawal of the species election with respect to the cardiovascular disorder.

The Examiner further states that rejections not reiterated from the previous Office Action have been withdrawn (Office Action, page 2). Applicants thank the Examiner for the withdrawal of the following rejections (since such rejections are not reiterated in the Office Action):

- claims 2-4, under 35 U.S.C. § 112, second paragraph, allegedly having insufficient antecedent basis;
- claims 2, 3, 5, 7-9, 11, 13, and 14, under 35 U.S.C. § 112, second paragraph, as allegedly indefinite;
- claims 15-23, under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement;
- claims 5-9 and 11-13, under 35 U.S.C. § 103(a), as allegedly obvious over Gumkowski et al. (U.S. Patent Application Publication 2006/0014788) in view of Ault et al. (U.S. Patent 7,049,283);
- claims 5-9 and 11-13, under 35 U.S.C. § 103(a), as allegedly obvious over Shinkai et al. I (U.S. Patent 6,426,365) in view of Sanbar et al. (*Circulation*, Volume XXXVIII, October 1968);
- claims 1-9 and 11-23, for nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-24 of Shinkai et al. I (U.S. Patent 6,426,365) or Shinkai et al. II (U.S. Patent 6,753,346); and
- claims 1-9 and 11-23, provisionally for nonstatutory obviousness-type double patenting as allegedly unpatentable over (a) claims 1-18 of co-pending U.S. Patent Application 10/825,531, or (b) claims 1-5, 7-32, 34-52, and 54-83 of co-pending U.S. Patent Application 10/835,916.

Discussion of the Obviousness Rejection

Claims 1-9 and 11-23 allegedly are obvious over Gumkowski et al. in view of Ault et al. and Englert et al. Inasmuch as claims 9 and 11-14 have been canceled, this rejection is addressed with respect to claims 1-8 and 15-23.

The Office Action states that Applicants traverse the "instant rejection" and that the traversal has been fully and carefully considered in its entirety (Office Action, page 3, second and third full paragraphs). Applicants respectfully point out to the Examiner that the current

rejection over the combination of Gumkowski et al., Ault et al., *and* Englert et al. has not previously been applied to aforementioned claims. As such, heretofore, Applicants had not traversed this particular rejection.

Gumkowski et al. discloses hundreds of disparate CETP inhibitors – only one of which is *S*-[2-([[1-(2-ethylbutyl)cyclohexyl]carbonyl]amino)phenyl] 2-methylpropanethioate ("JTT-705") (see paragraphs 0113-1035). Ault et al. discloses the use of crospovidone but is not directed to the use of CETP inhibitors at all or the treatment of cardiovascular disorders. Englert et al. discloses the crystallization of a compound that is unrelated to JTT-705. In view of the unrelatedness of the disclosures of these references to each another, one of ordinary skill in the art would not be led to the combination of these references in the first place. In other words, if one of ordinary skill in the art had no prior knowledge of Applicants' invention, that ordinary artisan would not come to the conclusion that the disclosures of Gumkowski et al., Ault et al., and Englert et al. should be combined. To assert otherwise, ignores the unrelatedness of the cited references to each other and relies on improper and impermissible hindsight knowledge of Applicants' invention. The Office has not provided any support as to *why* one of ordinary skill in the art would consider and combine the disclosures of Gumkowski et al., Ault et al., and Englert et al.

In considering whether or not the present invention is unobvious over the combination of the cited references, the Office must avoid the improper use of hindsight reconstruction, namely utilizing the pending claims as a template for selecting particular portions of particular references to combine so as to yield the present invention without any consideration of what one of ordinary skill in the art at the relevant time actually would have faced in seeking to solve the problem at hand. As eloquently stated by the Federal Circuit: "Care must be taken to avoid hindsight reconstruction by using 'the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit." *Grain Processing Corp. v. American Maize-Products Corp.*, 840 F.2d 902, 5 U.S.P.Q.2d 1788 (Fed. Cir. 1988).

In any event, even when the combination of Gumkowski et al., Ault et al., and Englert et al. is considered, if anything, the cited references tend to demonstrate the unobviousness of the present invention as defined by the pending claims. For example, Gumkowski et al.

demonstrates that there are *many* options available to one of ordinary skill in the art in selecting an appropriate CETP inhibitor. By focusing on the crystallization of particular compounds, Englert et al. effectively points out that crystallization techniques are not universally applicable to all types of compounds. Moreover, Ault et al. evidences the problems in selecting appropriate agents for pharmaceutical compositions by describing that the types of agents for the compositions described therein are "susceptible to cleavage by acids and enzymes in the gastro-intestinal tract" (col. 2, lines 43-49). In particular, Ault et al. contends that an additive such as crospovidone or povidone will maintain the integrity of these agents susceptible to cleavage, thereby increasing their bioavailability. This teaching in Ault et al. constitutes a teaching away from using an additive such as crospovidone in a formulation comprising a compound that *must* cleave *in vivo* to form an active agent. Thus, upon reading the disclosure of Ault et al., one of ordinary skill in the art would not be motivated to use the additive described therein in combination with JTT-705 because JTT-705 *must be* hydrolyzed *in vivo* to form the active agent. See the specification at, for example, paragraph 0076. As a result, even if it were assumed that an ordinary artisan would select JTT-705 from Gumkowski et al. and then seek out additional references for teachings on how to increase the bioavailability of JTT-705, that ordinary artisan would not rely upon the disclosure of Ault et al. because Ault et al. teaches that crospovidone will prevent a compound from cleaving *in vivo*.

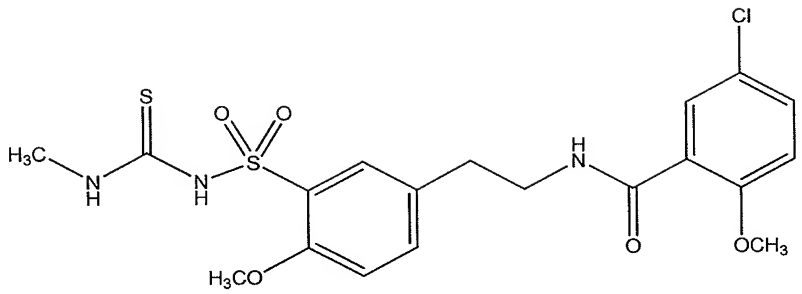
The Office Action includes comments that refer to specific claims, and these comments are addressed by Applicants below.

With respect to claim 2, the Office Action points out that Gumkowski et al. discloses that the CETP inhibitor can be provided in a formulation in 1-5 wt% (Office Action, page 4, first full paragraph). Applicants note that paragraph 0049 of Gumkowski et al. actually discloses that the amount of CETP inhibitor in a formulation can be 1-50 wt%. Nonetheless, this disclosure of Gumkowski et al. has nothing to do with the feature recited in claim 2. In particular, claim 2 is directed to a composition in which more than 50% of the cholesteryl ester transfer protein inhibitor is crystalline. Thus, claim 2 requires that at least 50% of the CETP inhibitor is crystalline, which is completely unrelated to the amount of a CETP inhibitor that may be present in a formulation. Gumkowski et al. does not teach or suggest an

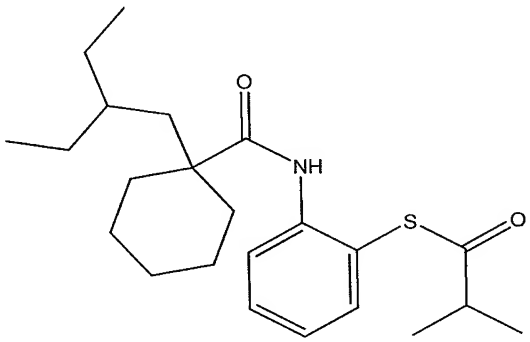
embodiment in which at least 50% of *any* of the CETP inhibitors described therein are crystalline, let alone JTT-705, as required by claim 2.

On page 4 (second full paragraph), the Office Action states that claims 2-6 and 12 are drawn to "the elected compound and crospovidone in crystalline form." It is noted that in claims 2-6 (as indicated above, claim 12 has been canceled), only the CETP inhibitor is required to be in crystalline form. The crospovidone (claims 2-4) or water-insoluble concentration-enhancing additive (claims 5 and 6) is not required to be crystalline.

As regards claims 2-6, the Office alleges that it would have been obvious to use the crystallization techniques of Englert et al. because Englert et al. teaches a benzamide structure. However, simply because the compound disclosed by Englert et al. has a benzamide functional group (among several other functional groups), it cannot be asserted that such common functional group has any relevance whatsoever to the compound of the pending claims. Overall, the compounds of Englert et al. and the pending claims are quite unrelated to one another, as is immediately apparent by a consideration of the structures of the compounds, which are set forth below for convenience. Indeed, the Office has not made any analysis to compare the two structures beyond merely citing to the benzamide moiety. In view of the structural differences between the compounds, one of ordinary skill in the art would not reasonably believe that any technique described in Englert et al. would be applicable to a compound such as JTT-705. In other words, the mere presence of a benzamide group in JTT-705 would not cause one of ordinary skill in the art to reasonably believe that the crystallization technique disclosed in Englert et al. could be applied with success to JTT-705.



Englert et al.



JTT-705

The Office comments on the term "about" in claims 7-13 to allege that the term encompasses any functional amount provided that the remainder of "the claim embodiment limitations" are anticipated by the prior art reference (Office Action, page 4, third full paragraph). Applicants are confused by this statement because the current rejection is not an anticipation rejection, and the specific prior art reference that allegedly "anticipates" the cited claims is not recited.

With respect to method claims 18-23, the Office contends that "the instantly claimed method is inherently taught by the reference" (Office Action, page 4, fourth full paragraph). Again, "the reference" is not identified. Moreover, the Office's comments regarding inherency may be appropriate to an anticipation rejection (which has not been set out in the Office Action) but are not appropriate to an obviousness rejection (which is at issue here).

The Office Action further states on page 4 (fourth full paragraph) that the burden has shifted to Applicants to prove that the subject matter of the prior art does not have the relied upon characteristic. Applicants respectfully point out to the Office that the burden of proof has not shifted to Applicants because the Office has failed to establish a proper *prima facie* case of obviousness for at least the reasons set forth above.

The Office Action also states that "Applicant's arguments fail to clearly point out the patentable novelty which he thinks the claims present in view of the state of the art disclosed by the reference cited" (Office Action, page 5, first full paragraph). However, contrary to the Office's assertion, the pending claims are novel inasmuch as no anticipation rejection has been made.

The Office Action further states that Applicants "fail to specifically point out disagreements with the Examiner's contentions and/or how the claims avoid the reference or are distinguishes [sic] from the same and are, therefore clear not persuasive in establishing the evidence of novelty outweighs that proffered to support the instant conclusion of a lack of novelty" (Office Action, page 5, first full paragraph). Applicants are unclear as to the meaning of this statement. Firstly, in the reply to the previous Office Action as well as herein, Applicants have pointed out disagreements with the Examiner's contention about the alleged obviousness in view of the cited references. Secondly, the Office again raises the concept of novelty, which is inapplicable to the obviousness rejection in issue here.

In view of the foregoing, Applicants maintain that the present invention is unobvious over the combination of Gumkowski et al., Ault et al., and Englert et al. Accordingly, Applicants submit that the obviousness rejection is without merit and should be withdrawn.

Discussion of the Obviousness-type Double Patenting Rejection

Claims 1-9 and 11-23 have been rejected for nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-24 of Shinkai et al. II in view of Ault et al. The claims of Shinkai et al. II do not teach or suggest (a) a pharmaceutical composition comprising JTT-705 and crospovidone (e.g., claim 1), (b) a pharmaceutical composition comprising (i) substantially crystalline JTT-705, in which the amount of inhibitor in amorphous form does not exceed about 10% and (ii) a water-insoluble concentration-enhancing additive (e.g., claim 5), or (c) a method for the treatment of a cardiovascular disorder by administration of a pharmaceutical composition comprising JTT-705 and crospovidone (e.g., claim 15), as recited in the pending claims. Since the claims of Shinkai et al. II do not teach or suggest a pharmaceutical composition comprising a water-insoluble concentration-enhancing additive, such as crospovidone, the Examiner relies on the disclosure of Ault et al.

Upon reading the claims of Shinkai et al. II, one of ordinary skill in the art would not know that there existed a need to increase the bioavailability of JTT-705 and as such would not know to seek another reference. Again, the Office uses an improper hindsight analysis to assert that one would know to search the literature and arrive at the disclosure of Ault et al. However, as discussed above, Ault et al. is not directed to the use of CETP inhibitors at all or the treatment of cardiovascular disorders. Therefore, even if, for some unknown reason an ordinary artisan would turn to a reference in addition to Shinkai et al. II, that artisan would not rely upon Ault et al. since the disclosure of Ault et al. is directed to unrelated compounds and unrelated disorders.

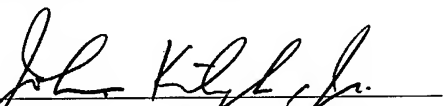
Moreover, as discussed above, Ault et al. teaches away from adding crospovidone to a formulation comprising a compound that must cleave *in vivo* to form an active agent. Accordingly, even if an ordinary artisan identified Ault et al. in the first place, she would have been led *away* from the subject matter of the pending claims by the disclosure of Ault et al.

In view of the foregoing, the subject matter of the pending claims cannot be considered obvious in view of the claims of the cited patent, and the obviousness-type double patenting rejection should be withdrawn.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

Respectfully submitted,



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Date: July 15, 2008